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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,693	02/02/2001	Mike A. Clark	PHOE-0060	9010

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,693	CLARK ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,27 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 6-7, 27, 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-2, 6-7, 27, 31-36 are examined in the instant application.

The following are the remaining rejections.

REJECTION UNDER 35 USC 103

Rejection under 35 USC 103 of claims 1-2, 6-7, 27, 31-36 pertaining to being obvious over US 5,804,183 in view of Takaku, H et al, 1995, Jpn. J Cancer Res, 86: 840-846, IDS# AM, in paper No:6, on 06/19/01, Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, remains for reasons already of record in paper of 01/12/05.

Applicant argues that Fipula (US 5,804,183) does not teach method for identifying a cancer susceptible to AD therapy by detecting the presence or absence of arginosuccinate synthetase (ASS), and that there is no motivation to combine the references.

Applicant's arguments in paper of 04/12/05 have been considered but are found not to be persuasive for the following reasons:

Although Fipula (US 5,804,183) does not teach method for identifying a cancer susceptible to AD therapy by detecting the presence or absence of arginosuccinate synthetase (ASS), the deficiency in Fipula is compensated by the secondary references.

Further, contrary to Applicant arguments, the motivation for combining the references is clear, i.e. to improve the chance of successful treatment.

In view that high susceptibility to cell killing by AD therapy is correlated with low level of ASS, as taught by Sugimura et al, and further in view that AD therapy has been successfully used for treating carcinoma, or melanoma, all of which are deficient in ASS, as taught by Fipula et al, it would have been obvious to identify or screen for cancers that are susceptibility to AD therapy, by determining the level of ASS in patients having the cancers.

The motivation of doing so is to improve the chance of successful treatment, in view that not all cancers are susceptible to AD therapy, because the AD sensitivity of various tumor cells is attributed to the reduced level of argininosuccinate synthetase expression, as taught by Sugimura et al.

Applicant argues that Takaku teaches that arginine deiminase (AD) effectively depletes cells of arginine, and that the effect of AD is not an increased level of citrulline in the media. Applicant argues that Takuku does not teach that any cell type is deficient in ASS, nor tumors of any types are deficient in ASS.

The Examiner takes note that Arginine is well known to be necessary for cell growth, and that Arginine is normally synthesized or supplied from citrulline by the enzyme ASS (Sugimura, p.193, second column, first paragraph, Takaku, figure 1 on page 841). In view of the teaching of the mechanism of AD cell killing, i.e. by depleting Arginine, as taught by Takaku, it is clear that cells that are deficient in ASS more likely would have low level of Arginine as compared to cells that have normal level of ASS,

which could supply Arginine from citrulline, and therefore, would be more susceptible to the depletion of Arginine, and consequently cell killing, by AD therapy.

Further, the fact that Takuku does not teach that any cell type is deficient in ASS, nor tumors of any types are deficient in ASS is expected, because it is known in the art that not any cancers are susceptible for AD treatment, and thus more likely, not any cancers would have depletion in ASS. Further, Applicant is reminded that the claimed method is a method for identifying cancer cells susceptible for AD therapy, by screening tested cancer cells for their deficiency in ASS, wherein it is not known previously which of these cancer cells are deficient in ASS. In addition, in view of the existence of different cancers that have deficiency in ASS, such as carcinoma and melanoma, as taught by Fipula, and in view that AD have been successful in treating several different cancers, such as sarcoma, melanoma, colon carcinoma, and hepatoma, in addition to four kinds of tumor cell lines, and further in view of a correlation between high sensitivity of cell killing by AD and low level of ASS, one would have expected that this lack of ASS is not confined to a single type of cancer.

Applicant argues that Sugimura only teaches that certain melanoma cells which are susceptible to arginine depletion therapy are also deficient in ASS. Applicant argues that not all melanoma cells that are susceptible to AD are completely ASS deficient, such as one cell line, GG361. Applicant argues that at best, Sugimura teaches that a handful of melanoma that are highly sensitive to AD therapy are also ASS deficient.

Contrary to Applicant's arguments, based on the teaching of Sigumura, and in view of the mechanism of action of AD treatment, and the activity of the enzyme ASS,

one would conclude that there is a clear correlation between sensitivity of AD treatment and low level of ASS gene expression.

Sugimura teaches that Arginine is essential for the survival and propagration of many mammalian tissues (p.193, second column, first paragraph), and that as **expected** (emphasis added) from their sensitivity to AD treatment, except for one cell line, G361, among the five melanoma cell lines studied, all four melanoma cell lines that are highly sensitive AD also have low level of ASS (p.194, second column, paragraph under Discussion, figure 2 on page 194). This correlation between sensitivity of AD treatment and low level of ASS gene expression is found not only in the melanoma cell lines studied, but is found as well in normal cells having low ASS, in view of the teaching of Sugimura that "human peripheral blood lymphocytes are highly sensitive to the cell growth inhibitory activity of AD in vitro **because** (emphasis added) of their extremely low level of expression of the ASS gene" (p.191, second column, last four lines bridging p.192). This correlation is further confirmed by the fact that similar to the control cell line TL-Mor, the cancer cell line Hela, that has high level of ASS, is not sensitive AD treatment, (Sugimura et al, p.194, first column, last paragraph, and figure 2 on page 194).

Further, although the melanoma cell line G361, having a relatively high level of ASS expression, is sensitive to AD, however, the level of sensitivity to AD treatment is much less than that of the other four melanoma cells that have low level of ASS. That is, G361 requires a much higher level of concentration of AD, at 130 ng/ml to show a reduction to 23% of control cell proliferation, as compared to a level of 16 ng/ml, or 32

ng/ml of AD, which almost completely inhibits cell proliferation of the other four melanoma cell lines.

Moreover, this correlation is expected by understanding the mechanism of AD cell killing, i.e. cell killing by depleting Arginine, taught by Takaku, and by understanding the activity of ASS, an enzyme that supplies Arginine to the cells, and would replenish any decrease in the level of Arginine in the cells. That is, cells that are deficient in ASS more likely would have low level of Arginine as compared to cells that have normal level of ASS, and therefore, would be more susceptible to the depletion of Arginine, and consequently cell killing, by AD therapy.

Applicant argues that Filpula teaches only that certain sarcomas that are deficient in ASS, especially citing the melanoma described by Sugimura, nitric oxide-related conditions and certain dietary conditions are treated, because they have the same underlying mechanism which responds to arginine deprivation. Applicant argues that Fipula does not state that any tumor with ASS deficiency would respond to arginine deficiency. Applicant argues that nowhere does Fipula makes that connection, and that Fipula merely suggests that specific tumors, known to respond to arginine deprivation, would be expected to respond favorably to *Mycoplasma arthriditis* arginine deiminase conjugate therapy. Applicant argues that Filpula does not suggest that ASS deficiency in and of itself is predictive of which tumors would respond to arginine deprivation therapy.

The arguments are not found to be persuasive.

Contrary to Applicant's argument, claim 7 in Fipula et al clearly teaches a method for treating "a cancer", i.e. any cancer, using the AD therapy. Moreover, One would have expected that the AD treatment by Fipula would be successful for any cancers that are deficient in ASS, in view of the teaching of the mechanism of AD cell killing, i.e. by depleting Arginine, as taught by Takaku, and it is clear that cells that are deficient in ASS more likely would have low level of Arginine as compared to cells that have normal level of ASS, and therefore, would be more susceptible to the depletion of Arginine, and consequently cell killing, by AD therapy, supra, and further in view that not only carcinoma and melanoma cells that have low level of ASS gene expression are susceptible to AD treatment, as taught by Fipula et al, and Sugimura et al, but normal cells such as human peripheral blood lymphocytes that have low level of ASS are also susceptible to AD treatment, as taught by Sugimura et al.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
June 06, 2005